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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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TOWNSEND AND TOWNSEND AND CREW, LLP
TWO EMBARCADERO CENTER
EIGHTH FLOOR
SAN FRANCISCO, CA 94111-3834

EXAMINER	
PITRAK, JENNIFER S	

ART UNIT	PAPER NUMBER
1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/572,932	NAKAMURA ET AL.	
	Examiner	Art Unit	
	JENNIFER PITRAK	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 April 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *16,21 and 25-29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *16, 21, 25-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Remarks

In the response filed 04/30/2008, Applicants amended the specification, amended claims 16, 21, and 25, canceled claims 1-15, 17-20, 22-24, and added new claims 26-29. Claims 16, 21, and 25-29 are pending and are under examination.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Objections to the Specification - MAINTAINED

The objections to the specification set forth in the Office Action mailed 02/06/2008 are maintained because the amendments to the specification have not remedied the presence of hyperlinks in the specification. It is recommended that the prefix, "www." be removed from the reference to website addresses.

Claim Rejections - 35 USC § 112 - MAINTAINED

The amendment to claim 21 has obviated the rejection of claim 21 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement.

Claims 16, 27, and 28 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This rejection is maintained for the reasons of record and as further described.

The claims are to *in vivo* methods of treating disease in a subject by administering an siRNA targeting *MGC47816* (claim 16 and 27) and to compositions intended for such methods (claim 28). The pharmaceutical use of the compositions claimed in claim 28 is addressed in this rejection. According to MPEP 2164.01(c), when a compound or composition claim is limited by a particular use, enablement of that claim should be evaluated based on that use. Thus, claim 28 is currently being evaluated on enablement for a therapeutic use of the claimed composition, like the method claim, claim 16. The removal of "pharmaceutical" from claim 28 would obviate the enablement rejection of this claim.

The nature of the instantly claimed methods, comprising administration of an siRNA targeting *MGC4781* to provide a treatment effect, *in vivo*, is subject to the considerations and limitations of nucleic acid therapeutics as discussed further below. Claim 28, directed to a pharmaceutical composition,

The state of the art at the time of filing, relative to the enablement of nucleic acid-based therapies *in vivo*, recognizes that there is a high degree of unpredictability in the art due to obstacles that continue, to the present day, to hinder the therapeutic application of nucleic acids *in vivo* (whole organism) including, for example, problems with delivery and target accessibility. The following references discuss the problems of nucleic acid based therapies in reference to the claimed therapeutic siRNA method.

Kalota, *et al*. (2006, of record), published years after the instant filing date, provides a review of the challenges that remain before nucleic acid therapy becomes routine in therapeutic settings and indicate that achieving an effective nucleic acid therapy requires significant trial and error. For example, according to Kalota et al., "a significant obstacle to be overcome [in employing antisense nucleic acids for post-transcriptional gene silencing] is the delivery of

antisense molecules into cells." (p. 183). On page 184, Kalota, *et al.* explain that in their laboratory, although they have successfully used nucleoporation for delivery of siRNAs into suspended cells *in vitro*, the same delivery methods *in vivo* in animal systems and clinical applications is limited (first paragraph). The authors further indicate that delivery to specific target sites has been problematic due to the non-specific interactions of delivery complexes with blood components and non-target cells.

Given this unpredictability, in particular in regard to targeting and delivery of nucleic acid compounds (siRNA molecules), the skilled artisan would require specific guidance to enable the claimed methods for inhibiting expression of *MGC47816* in a subject *in vivo*, as claimed. The instant specification does not show how one skilled in the art might overcome the obstacles to providing nucleic acid therapy of the instantly claimed methods or how applicant has overcome the same general obstacles to nucleic acid therapy in the instant invention.

Furthermore, the claims are directed to treatment of cancer (HCC). The instant specification provides no support for cancer treatment, but only provides evidence of inhibiting growth of cultured cancer cells (Alexander and HepG2) *in vitro*. Therefore, the skilled artisan would have to perform a large and undue quantity of experimentation to perform the instantly claimed methods of treating cancer in a subject.

With regard to the amount of direction or guidance presented, the specification as filed does not provide sufficient guidance or instruction that would teach one of skill in the art how to successfully practice the instantly claimed methods. The specification discloses examples of administration of siRNAs targeted to *MGC47816 in vitro* to cultured cells and that such administration inhibits expression of the targeted *MGC47816* (p.38). Applicants, therefore, set forth the assumption that these *in vitro* effects translate to an effect in a subject with siRNAs

targeting *MGC47816* but provide no evidence to support this assumption. The specification does not show or demonstrate how the *in vitro* reduction of *MGC47816* in cultured cells leads to an effect in a subject.

In regard to the amount of experimentation that would be required to enable the instantly claimed methods in their full scope, the specification does not provide sufficient and specific guidance that would enable the skilled artisan to make and use the claimed methods of treatment in their full scope, without performing a large quantity of *de novo*, trial and error experimentation. This undue, *de novo* trial and error experimentation would require, at a minimum, how to *in vivo* deliver the siRNA to a target cell and have the claimed effects of treating hepatocellular carcinoma. These determinations would be required to be performed to enable any method of inhibiting expression of *MGC47816* in a subject, let alone a method of treating cancer. No specific guidance is provided in the specification that would allow a determination of the appropriate and successful modes of delivery *in vivo* such that the claimed siRNA could be provided, at a significant level for a sufficient amount of time to produce an effect as claimed.

Given the unpredictability in the field of siRNA, the experimentation required to enable the instantly claimed invention, commensurate with the full scope of what is claimed, would not be routine, as evidenced by the state of the art which considers that delivery to provide an *in vivo* treatment effect must be determined empirically (as set forth above). Based on the lack of specific guidance in the specification regarding the direction in which the experimentation should proceed, even if the *de novo* experiments required were considered routine by those of skill in the art (which they are not), the more or less standard nature of each experiment would be outweighed by the sheer quantity of *de novo* undue trial and error experimentation required to

determine how to practice the method of the instant invention. Moreover, even through such undue experimentation, the skilled artisan would not even expect to be successful for the broad scope of treatment as claimed.

In conclusion, due to the nature of the invention as a nucleic acid therapeutic for use *in vivo*, the degree of unpredictability in the art of nucleic acid-based therapy at the time the invention was made and even to the present day, the breadth of the claimed method as a method of inhibiting MGC47816 and treating HCC in a cell in a subject, the lack of disclosure of a representative number of species of method within the broad genus of methods of treatment as claimed, and the quantity of *de novo* trial and error experimentation necessary to discover the above, an undue amount of *de novo* trial and error experimentation would be required in order to practice the method of HCC treatment that is now claimed.

Therefore, the inventors have not enabled one skilled in the art to make and use the methods of the claimed invention.

Response to arguments

Applicant argues that the amendments to the claims to not only require a specific target sequence (e.g., SEQ ID NO: 19) but also to require a specific functionality (disruption of the expression of the MGC47816 gene and inhibition the function of the MGC47816 protein), eliminate the "trial and error" testing needed to identify functional siRNA oligonucleotides. Applicants argue that the scope of the amended claims and newly added claim 28, which is directed to a pharmaceutical composition comprising the claimed siRNA, clearly correlates with the scope of enablement (04/30/2008 response, p.8, second paragraph).

These arguments are not persuasive because the claims lack enablement for delivery and treatment effects *in vivo*, rather than for the inhibition of target gene expression, which is an inherent feature of siRNAs. Undue trial and error would be necessary to enable the claimed methods and intended use of the claimed compositions, which are to treatment of HCC in a subject.

Applicants further argue that, regarding *in vivo* efficacy, Applicants do not need to demonstrate that the invention is completely safe and Applicants need not show that a therapeutic process is enabled, but that all that is required is that a "reasonable correlation" exists between the scope of the claims and the scope of enablement. Applicants argue that they have conclusively demonstrated that MGC47816 is specifically up-regulated in hepatocellular carcinoma and that small interfering polynucleotides directed to the coding sequence of MGC47816, particularly SEQ ID NO: 19, can disrupt the expression of the gene and suppress the growth of hepatocellular carcinoma cells. Applicants then point to Li, et al. (submitted with 04/30/2008 response) as evidence that SNU449 cells are a reliable tool for predicting the effect of test agents in animals and that, therefore, their *in vitro* results enable the claimed methods and intended use of the claimed compositions.

These arguments have been considered but are not persuasive. First, the claims have been evaluated according to patent laws and have been found to lack enablement with regard to *in vivo* therapeutic results. The safety and FDA approval status are not factors in the instant analysis of the claims. Second, with regard to Applicants' arguments that a reasonable correlation has been established between Applicants' *in vitro* results and the *in vivo* therapy claimed, this is not persuasive because the Li reference demonstrates that injection of cancer cells results in less tumor growth from those injected cells if the cells have been treated with a

cyclin E-targeting siRNA. The Li reference does not teach a therapeutic use of siRNAs, but only teaches that a cultured population of cells behave similarly (reduced proliferation) when grown in culture in a petri dish or when cultured in an animal. This *ex vivo* evidence provided by the Li reference is not a reasonable correlation to treatment *in vivo*, which requires delivery, uptake, and a therapeutic effect of the siRNA in an animal. For these reasons and for the reasons of record, the claims to therapeutic methods and to compositions with a therapeutic intended use are not enabled.

Claim Rejections - 35 USC § 102 - MAINTAINED

Applicants' amendments to the claims to require the full length of SEQ ID NO: 19 have obviated the rejection of the previously presented claims. However, Claim 29 is rejected under 35 U.S.C. 102(e) as being anticipated by Khvorova, *et al.* (of record, US 2007/0031844).

The claim is to an siRNA targeting *MGC47816*, wherein the siRNA is 19-25 nucleotides in length.

Khvorova teaches siRNAs including an siRNA with the sense strand sequence, SEQ ID NO: 1564004, which is 19 nucleotides in length and targets *MGC47816* (SEQ ID NO: 1 in the instant application) at nucleotide positions 845-861. SEQ ID NO: 1564004 of Khvorova, et al. is 5'-CAGAACAAGGCAAGCAGTT-3' and is disclosed in priority document 60/502,050, filed 09/10/2003, in Table 5, which is incorporated by reference into 60/502,050.

Response to arguments

Applicants' amendments to the claims to require the full length of SEQ ID NO: 19 have obviated the rejection of the previously presented claims. Applicants argue that the Khvorova

reference does not pre-date the instant filing date. This is not persuasive because, as indicated above, the priority document, U.S. Provisional Application No. 60/502,050, filed 09/10/2003, contains tables that are incorporated by reference, table 5 of which contains SEQ ID NO:1564004.

Claim Rejections - 35 USC § 103 - NEW

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 21, 25, 26, 28, and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over UniGene cDNA library 3435 [online], Dias Neto, et al. (2000, PNAS, v.97:3491-6), Ambion [online], Bass (2001, Nature, v.411:428-9), and Elbashir, *et al.* (2001, EMBO J., v.20:6877-88), as evidenced by Entrez Gene [online].

The claims are to compositions comprising MGC47816-targeting siRNAs, including the siRNA with target sequence, SEQ ID NO: 19. MGC47816 is also known as FAM80A (Entrez Gene).

The UniGene database and the reference article therein, Dias Neto, et al. (2000, PNAS, v.97:3491-6), teach that the mRNA sequence of MGC47816 was known at the time of the instant application (UniGene database, Hs.420244, page 2). Dias Neto, et al. identified the sequence from cDNA isolated from human breast tumors (abstract).

The Ambion siRNA Target Finder program was available at the time of the instant application (see Ambion-siRNA-Target-Finder reference dated 2002) and the program generates an siRNA targeting the instantly claimed SEQ ID NO: 19 (see Target Sequence 23 in the Ambion-siRNA-MGC47816 reference).

It was well known at the time of filing of the instant application that siRNAs were extremely useful for "knocking down" gene expression by RNA interference (RNAi). Bass teaches that RNA interference, mediated by double-stranded small interfering RNAs (siRNAs), was very well-recognized as a very useful tool for studying gene function once the sequence of a gene is known, that RNAi was accessible to all scientists, and that RNAi is now routine in laboratories (p.428, first paragraph).

Elbashir also teaches that already in 2001, RNAi had rapidly developed into an important tool for reverse genetics and had been shown to be useful in mammalian cells if the siRNAs are less than 30 base-pairs in length (p.6878, second paragraph). They report their systematic analysis of length, overhangs, and sequence determinants of siRNA function. They conclude their report with guidelines for designing efficient siRNAs for inhibiting target gene expression (p.6855, "The siRNA user guide"). Elbashir, *et al.* describe efficient siRNAs as those duplexes

composed of 21-nt sense and 21-nt antisense RNAs that form a 19-bp double helix with 2-nt 3'-overhanging ends. The authors further explain that target recognition is highly sequence-specific and is mediated by the siRNA complementary to the target, the 3'-most nucleotide of the guide siRNA does not contribute to the specificity of target recognition, while the penultimate nucleotide of the 3'-overhang affects target RNA cleavage and a mismatch reduces RNAi 2- to 4-fold, and that the 5'-end of the guide siRNA can have more mismatches to the target RNA when compared with the 3'-end. The authors further explain that nucleotides in the center of the siRNA are important for siRNA specificity determinants, the relative orientation of the siRNA duplex in the endonuclease complex determines the strand that can be used for target recognition, and give recommendations for the types and sequences of the 3'-overhanging sequences to ensure that the desired siRNA strand is the mRNA targeting strand. The authors describe that asymmetry in the siRNA-endonuclease complex or the target site sequence or accessibility of the target RNA may cause variation in efficiency of siRNA activity. Elbashir, *et al.* clearly demonstrate variation in siRNA efficiency for target inhibition and set forth guidelines for the design of siRNAs. On page 6886, in their concluding remarks, Elbashir, *et al.* indicate that their results are important for the design of efficient siRNAs for silencing genes in *Drosophila melanogaster* and they provide a basis for similar studies in other organisms.

It would have been obvious to one of skill in the art at the time of filing of the instant application to make siRNAs to inhibit MGC47816 expression. UniGene and Dias Neto, et al. teach that the MGC47816 mRNA sequence was known and was identified from human breast tumors. When the MGC47816 cDNA sequence is used in the Ambion siRNA Target Finder program, which was available at the time of the instant application, the instant SEQ ID NO: 19 is provided as an siRNA target sequence. Furthermore, because both Bass and Elbashir *et al.* teach

the ubiquitous use within the scientific community of siRNAs for interfering with gene expression, one of skill in the art would immediately recognize siRNAs as an easy and routine way to inhibit MGC47816 gene expression for *in vitro* functional studies of the gene. Bass and Elbashir also make it clear that production of any siRNA sequence, including the instantly claimed SEQ ID NO: 19, would be a matter of routine experimentation and optimization, as Elbashir set forth siRNA design guidelines. Thus, the instant claims would have been obvious to one skilled in the art at the time of filing of the instant application.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JENNIFER PITRAK whose telephone number is (571)270-3061. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM, EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Jennifer Pitrak, PhD
Examiner
Art Unit 1635

/Tracy Vivlemore/
Primary Examiner, Art Unit 1635